REMARKS

Each rejection raised by the Examiner is addressed separately below. In view of the remarks discussed below, Applicants respectfully request reconsideration of the merits of this patent application.

Status of the Claims

Claims 1 and 4-23 are pending. Claims 2 and 3 are cancelled. Claims 18-23 have been withdrawn. Claims 1, 12, and 13 are currently amended.

Claim 1 specifies that a BHB is formed by hybridizing the target molecule with an oligonucleotide designed to form a BHB conformation. Support for this amendment may be found throughout the specification, at least for example in Figures 3 and 4.

Claim 12 specifies that the target RNA molecule and a second RNA molecule form a BHB conformation. Support for this amendment may be found throughout the specification, at least for example in Figures 3 and 4.

Claim 13 specifies that the second RNA molecule comprises a sequence that is at least partially complimentary to the target RNA molecule. Support for this amendment may be found throughout the specification, at least for example in Figure 4, which is a diagram of BHB-mediated trans-splicing. A skilled artisan understands that in order to achieve the mRNA pairing depicted in Figure 4, the target and targeting strands must exhibit at least partially complementary sequences to one another. Sequence complementarity within a BHB conformation is illustrated in Figures 5 and 8.

No new matter has been added.

Claim Rejections Under 35 U.S.C. § 112, Second Paragraph

Claims 1 and 4-17 stand rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specifically, the Examiner alleged that the precise structure of the final BHB conformation created from the claimed methods is unclear. Applicants understand that the Examiner interpreted the previous claims to encompass a BHB conformation wherein the single strand of target RNA contains both bulges, which allegedly is inconsistent

with the description of the BHB conformation provided in the specification (*i.e.*, one bulge in one strand and one bulge in the other, opposite strand [0035]).

Without agreeing with the Examiner's rejection, or acquiescing, but in the interest of expeditious prosecution, Applicants hereby amend independent Claims 1 and 12 to specify that the claimed bulge-helix-bulge conformation is formed when the target RNA is combined with either an oligonucleotide (Claim 1) or a second RNA molecule (Claim 12). Support for these amendments may be found throughout the specification, at least for example in Figures 3 and 4. Applicants also amend Claim 13 to specify that the second RNA molecule comprises a sequence that is at least partially complimentary to the target RNA molecule. Support for this amendment may be found throughout the specification, at least for example in Figure 4, which is a diagram of BHB-mediated trans-splicing. A skilled artisan understands that in order to achieve the mRNA pairing depicted in Figure 4, the target and targeting strands must exhibit at least partially complementary sequences to one another. Sequence complementarity within a BHB conformation is illustrated in Figures 5 and 8. Applicants respectfully request withdrawal of this rejection.

Claim Rejections Under 35 U.S.C. § 112, First Paragraph

Claims 1 and 4-17 stand rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. Specifically, the Examiner alleged that the claimed method is broader than the method disclosed in the specification, and given the level of unpredictability in the art, the specification allegedly does not indicate Applicants were in possession of the claimed "genus" (*i.e.*, cleavage *in vitro* and *in vivo*; cleavage of both endogenous and exogenous target mRNAs in cells; and use of archael or eukaryotic endonucleases).

The Examiner acknowledged that the specification describes artificial introduction of a BHB conformation-containing structure into a FLAG-EGFP construct (FIGs. 6-12). The Examiner also noted that FIG. 14 demonstrates a target cleavage method corresponding in scope with the instant claims (exogenous target mRNA, cleavage *in vitro* using an archael endonuclease). However, the Examiner alleges that the specification does not exemplify cleavage of endogenous target mRNAs in cells, nor does it exemplify cleavage of an RNA molecule by eukaryotic tRNA endonucleases. Applicants disagree.

As set forth in 35 USC § 112 and the MPEP, Applicants are in no way required to define "**all**" attributes of "**all**" species falling within a claimed genus in order to satisfy the dictates of §112, first paragraph. In fact, Applicants aren't even required to disclose a single species to satisfy the definition of an entire genus.

35 USC § 112, first paragraph requires nothing more than that the specification enables a person of ordinary skill in the art how to make and use the claimed invention. *In re Fisher*, 166 USPQ 18, 24 (CCPA 1970). **How** that teaching is provided **is not** dictated by the statutes, the regulations, the case law, or the MPEP. In fact, the MPEP specifically dictates that defining a generic term either by (1) listing a number of exemplary species that fall within the generic term; and/or (2) using broader terminology, are both perfectly valid and **approved** approaches to defining a generic term. See MPEP §2164.08. See also *In re Marzocchi*, 169 USPQ 367, 370 (CCPA 1971): "How a teaching is set forth, **by specific example** or **broad terminology**, is not important." (Emphasis added.)

As the Examiner concedes, the originally filed specification describes artificial introduction of a BHB conformation-containing structure into a FLAG-EGFP construct (FIGs. 6-12). The specification also provides a clear example (FIG. 14) of a target cleavage method corresponding in scope with the instant claims (exogenous target mRNA, cleavage *in vitro* using an archael endonuclease). As set forth in *In re Robbins*, 166 USPQ 552 (CCPA 1970), Applicants are not required to disclose even a single working example in order to enable an invention. For instance, Applicants assert that upon reviewing the specification, a skilled artisan would understand that cleavage of endogenous target mRNAs and cleavage of RNA molecules by eukaryotic tRNA endonucleases is possible, and that after reviewing the specification, a skilled artisan could carry out such cleavage experiments without undue experimentation. Indeed, subsequent work from the inventor's laboratory clearly indicate that tRNAs can be used to recruit the endogenous tRNA splicing machinery in yeast (*i.e.*, eukaryote) to mediate mRNA slicing (see abstract of Di Segni *et al., PNAS* (2008) and p. 6793, col. 2, para. 2-3 of Anderson and Staley, *PNAS* (2008)).

Further, FIG. 3 of the instant specification shows that a eukaryotic endonuclease can recognize and cleave a non-tRNA molecule (*i.e.*, mouse profilin 1 mRNA) when the RNA is combined with another oligoribonucleotide forming a BHB. This result is predictive of further

experiments, wherein cleavage is achieved via a eukaryotic endonuclease and wherein endogenous mRNA is targeted.

Accordingly, Applicants submit that the as filed disclosure clearly provides an adequate teaching under 35 USC 112, first paragraph, both by broad terminology and specific example.

Further still, it is improper to reject a claim under §112, first paragraph for not reciting various details or factors which must be presumed to be within the level of ordinary skill in the art. Again, see MPEP §2164.08; see also *In re Skrivan*, 166 USPQ 85, 88 (CCPA 1970). Providing a description of cleavage of endogenous target mRNAs in cells, or cleavage of an RNA molecule by eukaryotic tRNA endonucleases, is not necessary for one of skill in this field. One of ordinary skill in the field of the present invention hardly needs a simplified roadmap regarding how to make and use the claimed invention other than the description and example provided in the originally filed specification.

Applicants accordingly submit that the originally filed specification provides a reasonably representative description regarding the cleavage *in vitro* and *in vivo*; cleavage of both endogenous and exogenous target mRNAs in cells; and use of archael or eukaryotic endonucleases, and provides an adequate teaching of how to make the invention. Withdrawal of this rejection is requested.

Summary

In view of the amendments and remarks above, reconsideration is respectfully requested. The application is believed to be in condition for allowance and allowance of the same is requested. If all the claims are not allowed, Applicants request a telephone interview with the Examiner and his supervisor.

Applicants have enclosed a Petition for a One-Month Extension of Time. The Commissioner is authorized to charge any fees under 37 CFR § 1.17 that may be due on this application to Deposit Account 17-0055. If further fees are necessary, please charge Deposit Account 17-0055. The Commissioner is also authorized to treat this amendment and any future reply in this matter requiring a petition for an extension of time as incorporating a petition for extension of time for the appropriate length of time as provided by 37 CFR § 136(a)(3).

Respectfully submitted,

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/Ann E. Rabe/

Ann E. Rabe, Reg. No. 56,697
Attorney for Applicants
QUARLES & BRADY LLP
411 E. Wisconsin Avenue
Milwaukee, WI 53202
P: 414-277-5613
F: 414-978-8712